# Human Autonomic and Cerebrovascular Responses to Inspiratory Impedance

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**Background:** We evaluated the influence of breathing through an inspiratory Impedance Threshold Device (ITD) on autonomic neural and cerebrovascular function.

**Methods:** Eight subjects breathed through a sham ITD (0 cmH$_2$O) and an active ITD (−7 cmH$_2$O) in the supine position. We recorded the ECG, finger photoplethysmographic arterial pressure, cerebral blood flow velocity, and muscle sympathetic nerve activity (MSNA). In a randomized, counterbalanced design, subjects breathed spontaneously and also breathed at a set cadence of 15 breaths/min (0.25 Hz) for 3 minutes each. Data were analyzed in both time and frequency domains.

**Results:** Breathing through the active ITD increased mean arterial pressure by ~5 mm Hg, heart rate by 2 bpm, and mean cerebral blood flow velocity by 10% ($p <$ 0.05) with no effect on MSNA or estimates of vagal-cardiac control ($p >$ 0.05). The active ITD did not affect oscillations of interbeat R-R intervals, arterial pressures, or cerebral flow velocities within the low frequency (LF) domain of the power spectrum ($p >$ 0.05). Cross spectral analysis revealed no effect of the active ITD on transfer function magnitudes among arterial pressures and R-R intervals, or between arterial pressures and cerebral blood flow velocities at the LF ($p >$ 0.05).

**Conclusions:** Our results demonstrate that the ITD increases arterial pressure, heart rate, and cerebral blood flow velocity independent of changes in autonomic cardiovascular control or dynamic cerebral autoregulation. Use of an active ITD in situations of acute central hypovolemia, such as during hemorrhage, may slow the progression to hemodynamic instability in bleeding patients who retain the ability to ventilate spontaneously and robustly.

**Key Words:** Hemorrhage, Resuscitation, Cardiovascular regulation, Cerebral blood flow velocity, Shock.

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Adequate systemic oxygen delivery and cerebral blood flow are fundamental criteria for slowing or preventing progression to hemodynamic collapse in bleeding patients with reduced cardiac filling.[1] Resistive breathing through an inspiratory Impedance Threshold Device (ITD) reduces intrathoracic pressure, thereby producing a vacuum in the thorax which increases ventricular preload.[2,3] Resistive breathing has been shown to increase heart rate, arterial pressure,[4,5] cardiac output,[2,5,6] cardiac index and stroke volume index[7] and systemic oxygen delivery to vital organs.[8,9] Preliminary data from our laboratory suggest that in humans, such enhanced hemodynamic responses may occur independent of changes in autonomic neural activity, but this hypothesis has not been tested specifically.[4]

In pigs, use of an ITD has been shown to decrease intracranial pressure, increase cerebral perfusion pressure, and increase cerebral blood flow during cardiopulmonary resuscitation after cardiac arrest.[10,11] Improved cerebral perfusion during ITD breathing in humans was suggested by an amelioration of symptoms associated with orthostatic intolerance after a squat-stand test designed to induce orthostatic hypotension.[12] Increasing or maintaining cerebral blood flow in bleeding patients could potentially slow the progression to hemodynamic collapse, but the effects of breathing through an ITD on cerebral blood flow in humans have not been reported.

The purpose of this study was to determine the effects in healthy humans of normal breathing through an active ITD on the autonomic modulation of cardiovascular and cerebrovascular function. We tested the hypothesis that the ITD increases arterial pressure, heart rate, and cerebral blood flow velocity, and that such increases are not associated with changes in autonomic cardiovascular control or dynamic cerebral autoregulation.

## METHODS
### Subjects

Eight subjects [seven male and one female; height, 176 cm (SD 4); weight, 80 kg (SD 7); age, 38 yr (SD 11)] volunteered to participate in this experiment. Subjects were healthy nonsmokers, and they refrained from autonomic stimulants such as exercise or caffeine for 48 hours before the

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study. During an orientation session preceding each experiment, the experimental protocol and procedures were explained and each subject was familiarized with the laboratory and personnel. The experimental procedures and protocols were reviewed and approved by the Research Review Committee of the U.S. Army Institute of Surgical Research and the Brooke Army Medical Center Institutional Review Board. Each subject provided written informed voluntary consent before participation.

## Measurements

Physiologic variables were measured when the subjects were in the supine position. Data were recorded with a four-lead ECG, a finger cuff to record beat-by-beat arterial pressure with finger photoplethysmography (Finometer, Finapres Medical Systems, Arnhem, the Netherlands), a 2-MHz Doppler probe positioned at a constant angle over the temporal window to record cerebral blood flow velocity from the right middle cerebral artery (DWL Elektronische Systeme, Sipplingen, Germany), and a tungsten microelectrode (Frederick Haer, Bowdingam, Maine) inserted into the peroneal nerve in the popliteal region behind the right knee to record muscle sympathetic nerve activity (MSNA) as described previously.[13] End-tidal $CO_2$ was measured on a breath-by-breath basis at the mouth with an infrared sensor (Gambro, Enström, Sweden), and inspiratory pressure was recorded with a pressure transducer (MKS Instruments, Andover, Mass.).

## Protocol

In the supine position, subjects breathed spontaneously for 3 minutes through a facemask to which either a sham device (0 $cmH_2O$) or an active ITD ($-7$ $cmH_2O$; Advanced Circulatory Systems, Inc. Eden Prairie, Minn.) was affixed (randomized and counterbalanced). After this, subjects breathed again for 3 minutes through the same sham or active ITD while maintaining their respiratory rate constant by breathing in time to a metronome set at a pace of 15 breaths per minute (randomized and counterbalanced).

## Data Analysis

Data were sampled at 500 Hz and recorded directly to computer with commercial hardware and software (WINDAQ, Dataq Instruments, Akron, Ohio). R waves generated from the ECG signal were detected and marked at their occurrence in time. Diastolic and systolic pressures, and diastolic and systolic flow velocities were subsequently marked from the Finometer and Doppler tracings. Mean cerebral blood flow velocity was calculated on a beat-by-beat basis by computer with the following equation:

$$V_{mean} = V_{min} + 0.4(V_{max} - V_{min})$$

Where $V_{max}$ is maximal velocity (systolic), $V_{min}$ is minimal velocity (diastolic), and $V_{mean}$ is mean velocity. This equation has been published previously.[14,15] We derived Gosling pulsatility as an index of cerebral vascular resistance by subtracting diastolic from systolic velocity and then dividing by mean velocity.[16] Increases and decreases in pulsatility index are associated with cerebral vessel constriction and dilation.[17]

Bursts of MSNA were detected and marked by computer based on amplitude (approximately 3:1 signal-to-noise ratio) and latency from the preceding (one removed) R wave to burst peak of $1.3 \pm 0.5$ s.[18] We quantified MSNA in bursts per min and as the number of bursts occurring during every 100 heart beats (to control for intersubject differences in heart rate).

Oscillatory patterns of cardiac interbeat intervals (R-R intervals), arterial pressures, and cerebral blood flow velocities were determined with fast Fourier power spectral analysis. Data were made equidistant by interpolating linearly and resampling at 5 Hz. Data were then passed through a low-pass impulse response filter with a cutoff frequency of 0.5 Hz. Three-minute datasets were fast Fourier transformed with a Hanning window to obtain power spectra. Spectral power was expressed as the integrated areas within the low-frequency (LF = 0.05 − 0.15 Hz) and high-frequency (HF = 0.15 − 0.4 Hz) ranges.[19]

We calculated the coherence among systolic arterial pressures and R-R intervals, and among mean arterial pressures and mean cerebral blood flow velocities by dividing the cross-spectral densities of the two signals by the product of the individual autospectra. At the LF where signals are coherent (i.e. $\geq 0.5$), transfer function magnitudes among systolic pressures and R-R intervals represent arterial baroreflex gain,[20] and the transfer function magnitudes among mean arterial pressures and mean cerebral blood flow velocities represent a frequency dependence of dynamic cerebral autoregulation.[21] The transfer function magnitude expressing arterial baroreflex gain was calculated by dividing the cross-spectrum of systolic pressure and R-R interval by the autospectrum of systolic pressure. The transfer function magnitude expressing the frequency relation of cerebral autoregulation was calculated by dividing the cross-spectrum of mean arterial pressure and mean cerebral blood flow velocity by the autospectrum of mean arterial pressure.[14,21,22] Transfer functions were considered valid and averaged at the LF and HF only when coherence values were $\geq 0.5$.[20]

## Statistical Analysis

We analyzed our data with commercial statistical software (SAS Institute, Cary, N.C.). Differences between the means of each dependent variable were tested with a two-way repeated-measures ANOVA with repeated measures on condition (sham ITD versus active ITD) and breathing protocol (uncontrolled versus controlled breathing). Exact *p* values were calculated for all statistical tests and reflect the probability of obtaining the observed or greater effect given only random departure from the assumption of no effects.

## RESULTS

Figure 1 shows a drawing of the ITD and a representative research volunteer. A summary of recorded physiologic signals is shown as representative tracings from one subject in Figure 2.

Complete data sets were obtained for all subjects (n = 8) with the following exceptions: The sympathetic nerve recording was lost during controlled frequency breathing in one subject, and adequate Doppler recordings from the middle cerebral artery could not be obtained in another subject.

Mean values for all dependent variables of interest are displayed in Tables 1 and 2. We detected no main effects for the influence of controlled breathing ($p > 0.05$), and we detected no interaction effects between breathing and ITD conditions ($p > 0.05$).
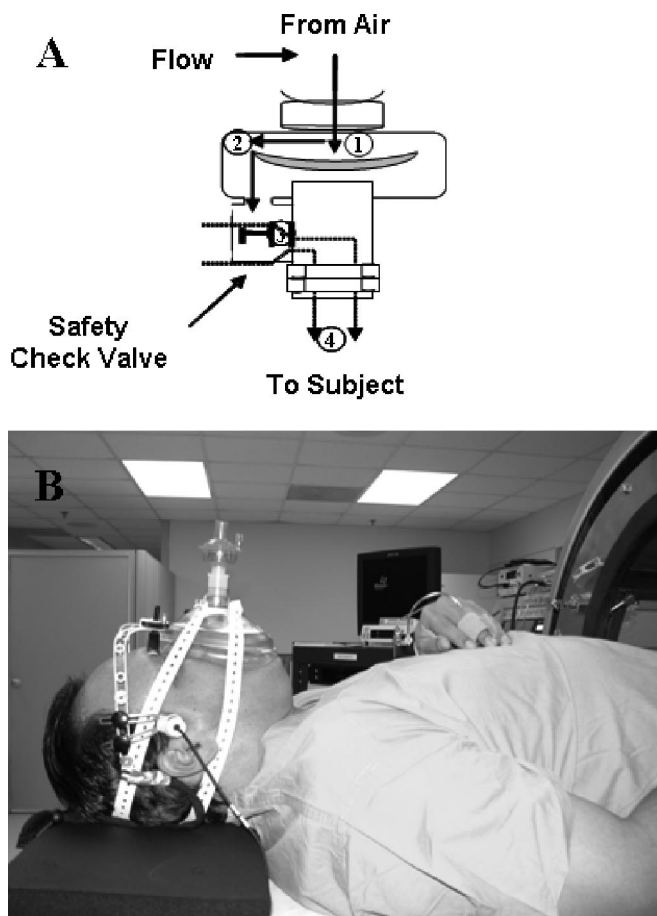


**Fig. 1.** *Drawing illustration (top panel A) of the Inspiratory Threshold Valve (ITV). During spontaneous inspiration, air flow from the ventilation port to the subject causes the silicone diaphragm to close (Step #1). The air flow bypasses the diaphragm to the Safety Check Valve (Step #2). When intrathoracic pressure reaches and exceeds the impedance threshold of the valve, the Safety Check Valve opens (Step #3) and air reaches the subject (Step #4). Panel B (bottom) shows a research volunteer instrumented with headgear housing the transcranial Doppler probe and the ITD consisting of the ITV connected to a facemask.*

Pooled across breathing conditions, we found that breathing through the active ITD increased heart rate [64 bpm (SD 11) vs. 66 bpm (SD 10); $p = 0.03$], and systolic [135 mm Hg (SD 7) vs. 143 mm Hg (SD 10); $p = 0.0005$], diastolic [75 mm Hg (SD 8) vs. 78 mm Hg (SD 6); $p = 0.01$], and mean [94 (SD 6) vs. 99 (SD 8) mm Hg; $p = 0.003$] arterial pressures. In conjunction with increases in heart rate, R-R intervals decreased with active ITD breathing [959 ms (SD 157) vs. 930 ms (SD 140); $p = 0.006$]. With the exception of systolic velocity [92 cm/s (SD 21) vs. 97 cm/s (SD 22); $p = 0.2$], breathing through the active ITD also increased cerebral blood flow velocity [diastolic 43 cm/s (SD 14) vs. 48 cm/s (SD 16); $p = 0.01$; mean 62 cm/s (SD 18) vs. 68 cm/s (SD 20); $p = 0.01$] and tended to decrease the pulsatility index [0.81 (SD 0.1) vs. 0.75 (SD 0.1); $p = 0.09$]. End-tidal $CO_2$ concentrations, taken as estimates of $Paco_2$, were 4.7% (SD 0.5) during sham breathing, and 4.6% (SD 0.6) during active ITD breathing ($p = 0.72$). A typical example of the effects of breathing through the active ITD on cerebral blood flow velocity is displayed graphically in Figure 3. In this subject (and all other subjects), removing the facemask and ITD valve caused rapid reductions in flow velocity with no change in arterial pressure as shown in Figure 4.

Breathing through the active ITD had no effect on MSNA or R-R interval oscillations at either the LF or HF ($p > 0.05$). Similarly, active ITD breathing did not affect LF arterial pressure or cerebral blood flow velocity oscillations ($p > 0.05$). However, at the HF mean arterial pressure oscillations [0.6 mm Hg$^2$ (SD 0.3) vs. 1.7 mm Hg$^2$ (SD 0.7); $p = 0.002$], and mean cerebral blood flow oscillations [0.8 cm/s$^2$ (SD 0.4) vs. 1.6 cm/s$^2$ (SD 0.9); $p = 0.005$] increased with active ITD breathing. Breathing through the active ITD decreased transfer function magnitudes among both systolic pressures and R-R intervals [22 ms/mm Hg (SD 16) vs. 11 ms/mm Hg (SD 7); $p = 0.01$] and mean arterial pressures and mean cerebral blood flow velocities [1.2 cm/s/mm Hg$^{-1}$ (SD 0.4) vs. 0.9 cm/s/mm Hg$^{-1}$ (SD 0.3); $p = 0.03$] at the HF.

Figure 5 shows a representative frequency domain analysis performed for the derivation of power spectra and subsequent transfer function used to assess arterial baroreflex gain and dynamic cerebral autoregulation. Cross spectral analysis revealed no effect of the active ITD on transfer function magnitudes among systolic pressures and R-R intervals [14 ms/mm Hg (SD 6) vs. 12 ms/mm Hg (SD 4); $p = 0.1$], or mean arterial pressures and mean cerebral blood flow velocities [0.9 cm/s/mm Hg$^{-1}$ (SD 0.3) vs. 0.8 cm/s/mm Hg$^{-1}$ (SD 0.3); $p = 0.7$] at the LF.

## DISCUSSION

We evaluated the influence of a low level of inspiratory impedance on human autonomic and cerebrovascular physiology and report two primary new findings: (1) active ITD breathing increases heart rate and arterial pressure through mechanisms other than vagal withdrawal and sympathetic
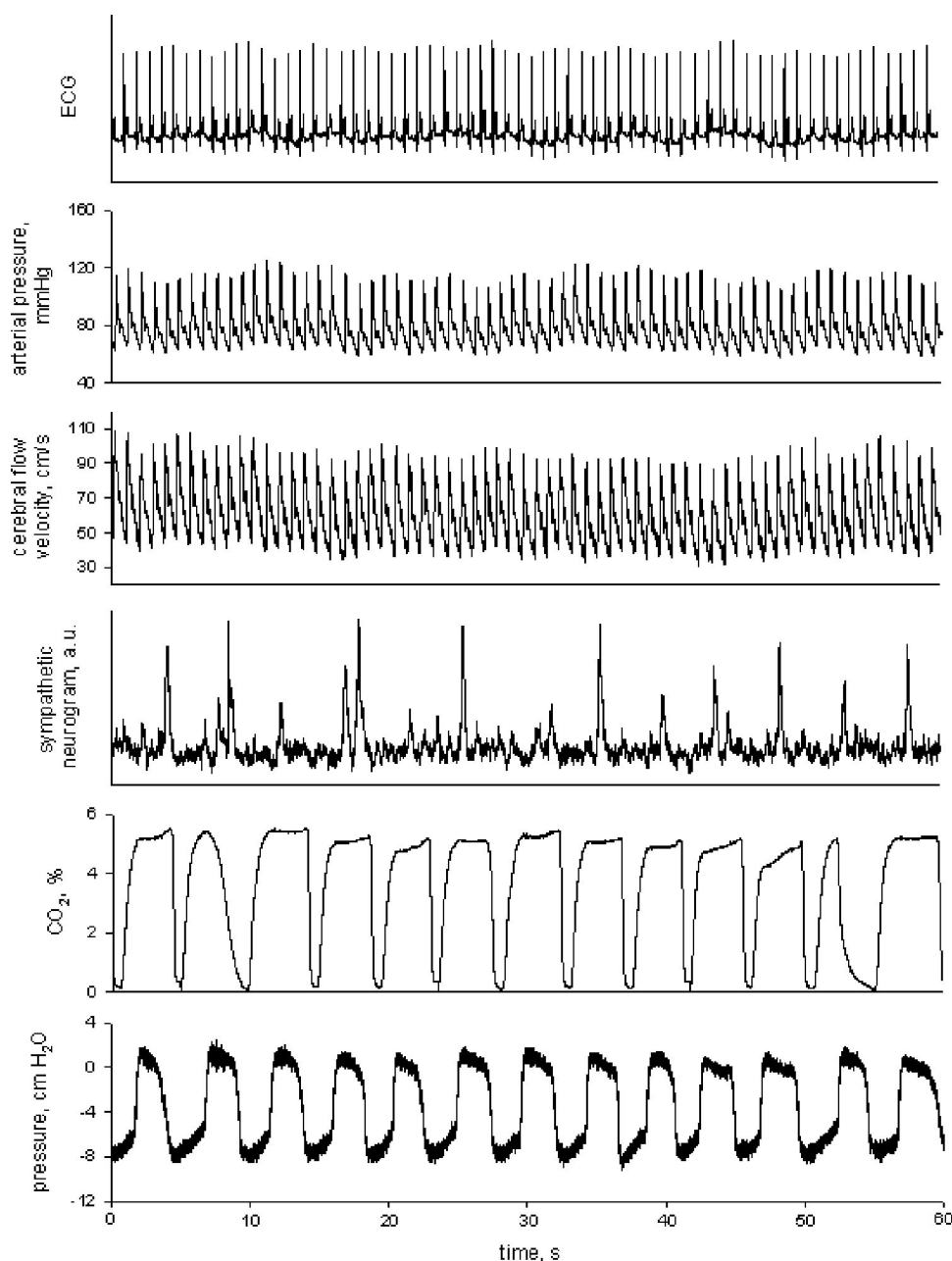
**Fig. 2.** *Original data tracings from one subject; pressure, active ITD pressure.*

activation; and (2) active ITD breathing increases cerebral blood flow velocity with no effect on dynamic cerebral autoregulation. We speculate that these enhancements may be conducive to slowing or preventing progression to hemodynamic instability under conditions of acute central hypovolemia in patients who retain their capacity to ventilate spontaneously and robustly.

## Controlling Breathing

Breathing frequency and depth may influence autonomic rhythms profoundly, and therefore investigators have suggested that for research purposes, breathing rate should be controlled strictly.[23] However, in this study we considered the effects of inspiratory impedance on systemic and cerebral hemodynamics from the perspective that breathing on an active ITD will be of benefit to patients suffering traumatic bleeding injuries. Victims of trauma clearly do not breathe at a set cadence, and so in the present study we investigated the effects of uncontrolled versus controlled breathing on responses to the active ITD. We detected no main effects for breathing protocol or interaction effects between the active versus the sham valve and breathing protocol (Tables 1 and 2). Therefore, we assessed the influence of the active ITD after pooling responses across breathing conditions.

**Table 1** Time Domain Data During Uncontrolled and Controlled Frequency Breathing With and Without an Inspiratory Impedance Device

| Variable | Uncontrolled Breathing | | Controlled Breathing | |
|---|---|---|---|---|
| | Sham ITD | Active ITD | Sham ITD | Active ITD |
| RRI, ms | 967 (159) | 927 (137)* | 951 (162) | 932 (151)* |
| pNN50, % | 23 (9) | 20 (10) | 19 (9) | 17 (8) |
| HR, bpm | 64 (12) | 66 (11)* | 65 ± 11 | 66 (10)* |
| SAP, mm Hg | 133 (9) | 140 (9)* | 137 (6) | 145 (11)* |
| DAP, mm Hg | 74 (8) | 76 (7)* | 75 (6) | 80 (8)* |
| MAP, mm Hg | 93 (7) | 97 (7)* | 95 (9) | 101 (9)* |
| $CO_2$, % | 4.9 (0.5) | 4.8 (0.3) | 4.6 (0.3) | 4.6 (0.3) |
| MSNA, b/min | 14 (8) | 16 (9) | 17 (9); n = 7 | 16 (8); n = 7 |
| MSNA, b/100hb | 22 (12) | 25 (15) | 27 (12); n = 7 | 24 ± 11; n = 7 |
| CFV-S, cm/s; n = 7 | 94 (22) | 96 (22) | 90 (22) | 98 (24) |
| CFV-D, cm/s; n = 7 | 45 (12) | 47 (16)* | 40 (15) | 48 (16)* |
| CFV-M, cm/s; n = 7 | 65 (17) | 68 (19)* | 59 (19) | 69 (21)* |
| PI, n = 7 | 0.78 (0.1) | 0.83 (0.2) | 0.75 (0.2) | 0.75 (0.1) |
| Resp, breaths/min | 12 (5) | 12 (5) | 15 (0) | 15 (0) |

Values are means with standard deviations in parentheses. Sham ITD, 0 $cmH_2O$ inspiratory resistance; Active ITD, −7 $cmH_2O$ inspiratory resistance; RRI, R-R interval; pNN50, the percentage of adjacent normal R-R intervals that vary by 50 ms or more, HR, heart rate, SAP, DAP, and MAP, systolic, diastolic, and mean arterial pressures; $CO_2$, end-tidal carbon dioxide, MSNA, muscle sympathetic nerve activity (b/min, bursts per minute; b/100 hb, bursts per 100 heart beats); CFV-S, -D, and M, systolic, diastolic, and mean cerebral flow velocity; PI, pulsatility index; Resp, respiration in breaths per minute; n = 8 unless specified otherwise; asterisk (*) denotes main effects for ITD breathing collapsed across conditions (uncontrolled and controlled breathing) where *p* values were ≤0.05.

**Table 2** Frequency Domain Data During Uncontrolled and Controlled Breathing With and Without an Inspiratory Impedance Device

| Variable | Uncontrolled Breathing | | Controlled Breathing | |
|---|---|---|---|---|
| | Sham ITD | Active ITD | Sham ITD | Active ITD |
| $RRI_{HF}$, $ms^2$ | 997 (580) | 552 (135) | 1101 (650) | 1019 (790) |
| $RRI_{LF}$, $ms^2$ | 1129 (619) | 1029 (552) | 429 (215) | 329 (154) |
| $SAP_{HF}$, mm $Hg^2$ | 2.4 (1.3) | 5.2 (1.4) | 3.1 (1.5) | 5.8 (1.4) |
| $SAP_{LF}$, mm $Hg^2$ | 6.2 (1.7) | 7.2 (1.7) | 3.9 (0.9) | 4.8 (1.8) |
| $MAP_{HF}$, mm $Hg^2$ | 0.5 (0.1) | 1.7 (0.3)* | 0.7 (0.2) | 1.7 (0.3)* |
| $MAP_{LF}$, mm $Hg^2$ | 2.7 (2.2) | 3.1 (1.1) | 1.6 (0.3) | 1.6 (0.3) |
| $CFV_{HF}$, $cm/s^2$; n = 7 | 0.68 (0.2) | 1.8 (0.4)* | 0.84 (0.2) | 1.4 (0.2)* |
| $CFV_{LF}$, $cm/s^2$; n = 7 | 2.7 (0.9) | 2.7 (0.7) | 2.2 (0.6) | 1.9 (0.5) |
| SAP-RRI-$TF_{HF}$, ms/mm Hg | 22 (12) | 12.7 (9)* | 22.6 (14) | 10 (6)* |
| SAP-RRI-$TF_{LF}$, ms/mm Hg | 14 (6) | 12 (4) | 14 (4) | 10 (4) |
| MAP-CFV-$TF_{HF}$, cm/s/mm $Hg^{-1}$; n = 7 | 1.1 (0.4) | .93 (0.2)* | 1.1 (0.2) | .93 (0.2)* |
| MAP-CFV-$TF_{LF}$, cm/s/mm $Hg^{-1}$; n = 7 | 0.88 (0.4) | 0.73 (0.4) | 0.84 (0.3) | 0.96 (0.4) |

Values are means with standard deviations in parentheses; Sham ITD, 0 $cmH_2O$ inspiratory resistance; Active ITD, −7 $cmH_2O$ inspiratory resistance; RRI-HF and RRI-LF, R-R interval spectral power at the high and low frequencies; SAP- and MAP-HF and -LF, systolic and mean arterial pressure spectral power at the high and low frequencies; CFV-HF and CFV-LF, cerebral flow velocity spectral power at the high and low frequencies; SAP-RRI-TF, systolic arterial pressure and R-R interval transfer function magnitude at the low frequency; MAP-CFV-TF, mean arterial pressure and mean cerebral flow velocity transfer function magnitude at the low frequency; n = 8 unless specified otherwise; asterisk (*) denotes main effects for ITD breathing collapsed across conditions (uncontrolled and controlled breathing) where *p* values were ≤ 0.05.

## Resistive Breathing and Autonomic Cardiovascular Regulation

Consistent with previous observations in human subjects,[5] we found that breathing through an active ITD increases both heart rate and arterial pressure. Concomitant increases in both heart rate and arterial pressure during resistive breathing seems to suggest an uncoupling or overriding of the arterial baroreflex, but Convertino et al.[4] found that ITD breathing preserves carotid baroreflex responses and shifts the sigmoid response curve to the right, toward higher arterial pressures. Similar to breathing

through an active ITD, physical exercise also decreases intrathoracic pressure, increases both heart rate and arterial pressure, and resets the carotid-cardiac baroreflex response curve to the right.[24] This exercise response is mediated, in part, by parasympathetic withdrawal and sympathetic activation.[25] We therefore speculated that the increased work of breathing through an active ITD might induce an exercise effect on heart rate and arterial pressure that would manifest as decreased time domain estimates of heart rate variability and HF R-R interval spectral power, and as increased MSNA. However, our data do not
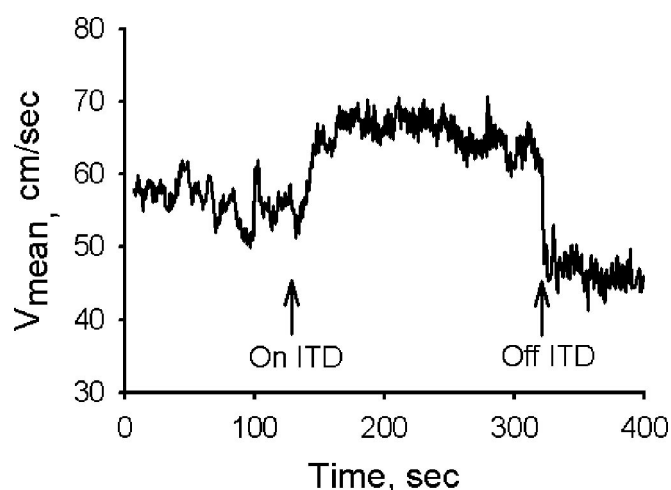
**Fig. 3.** *Original data tracing showing the effects of breathing on the active inspiratory Impedance Device (ITD; −7 cmH₂O) on mean cerebral blood flow velocity (V_mean).*
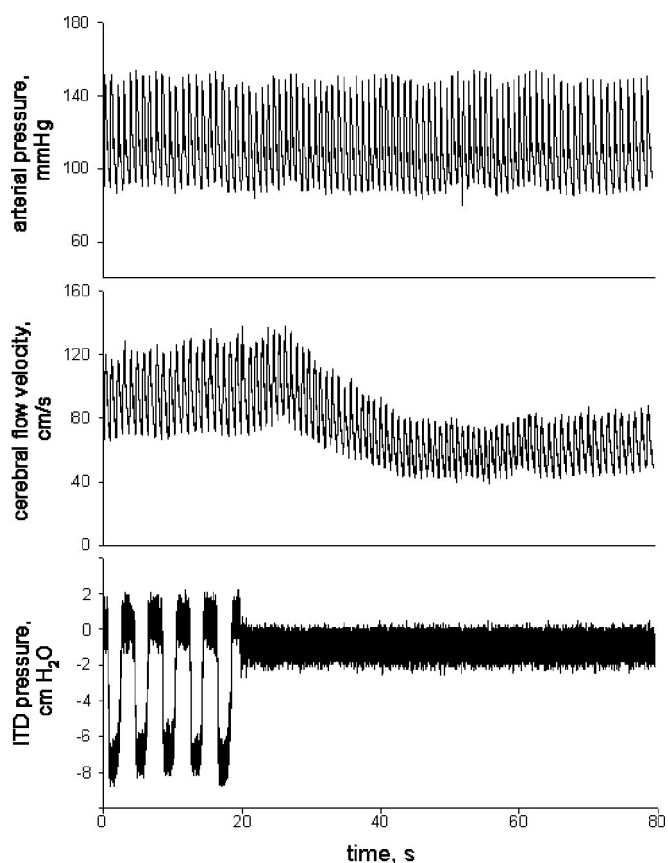


**Fig. 4.** *Acute reduction of cerebral flow velocity upon removal of the active ITD (−7 cmH₂O) shown in conjunction with arterial pressure.*

support this hypothesis. The percentage of adjacent R-R intervals that varied by at least 50 ms (pNN50; Table 1), and R-R interval oscillations at the HF (RRI$_{HF}$; Table 2), both adequate estimates of human vagal-cardiac control,[19] were unaffected by resistive breathing. In addition, direct recordings of MSNA re-

vealed that breathing through the active ITD had no effect on peripheral sympathetic traffic (Table 1). Although we did not record sympathetic traffic directly to the heart, MSNA measured from the peroneal nerve under resting condition correlates closely to norepinephrine spillover from the heart.[26]

Mechanical effects of enhanced cardiac filling may provoke chronotropic responses (i.e. the Bainbridge reflex) mediated through activation of atrial stretch receptors. The Bainbridge reflex, first reported in 1915,[27] describes a reflex tachycardia in response to volume loading of the right atrium in anesthetized dogs. Although not always demonstrable, at least two studies have provided evidence for the existence of the Bainbridge reflex in humans.[28,29] Heart rate increased after 500 mL saline infusion in conjunction with a reduction in R-R interval spectral power at the respiratory frequency, leading Barbieri et al.[28] to conclude that the Bainbridge reflex in humans is elicited by reduced vagal-cardiac modulation. However, mechanical stretch of the sinus node may cause heart rate to increase without necessarily engaging autonomic nerves,[30] and therefore specific mechanisms underlying the Bainbridge reflex in humans are complicated. Based on our results, the increased heart rates induced in the present study by resistive breathing cannot be attributed to reduced vagal-cardiac modulation (Tables 1 and 2). Although we did not measure myocardial dimensions, atrial distention in our subjects was probable since breathing on an active ITD increases stroke volume in resting supine humans.[5] It is possible that the magnitude of atrial stretch induced by breathing through the active ITD is less than that induced by 500 mL saline infusion,[28] and that the increased heart rate we observed was mediated through simple stretching of the sinus node. On the other hand, we cannot discount the possibility of selective sympathetic activation of the heart. For example, when atrial stretch in dogs was induced by balloon distention, single sympathetic fibers to the sinus node were activated, but sympathetic fibers normally activated by other stimuli such as arterial baroreceptor unloading[31] were silent. Because we recorded MSNA from a peroneal nerve at the periphery (i.e. efferent fibers activated importantly by arterial baroreceptor unloading[32]), our data do not address the possibility of selective sympathetic efferent activation specifically to the sinus node in response to breathing through the active ITD. With the limitation that we did not record sympathetic traffic to the sinus node, our results suggest that increases in heart rate and arterial pressure during resistive breathing occur independent of autonomic neural mechanisms.

Increased hemodynamic mechanical activation during resistive breathing is suggested by increases in both arterial pressure and cerebral blood flow oscillations at the HF (Table 2). The decreased transfer function magnitudes we observed among systolic pressures and R-R intervals, and among mean arterial pressures and mean cerebral blood flow velocities at the HF may reflect simply the influence of increased mechanical augmentation of arterial pressure rather than modulation by autonomic nerves. For example, partial coherence analysis
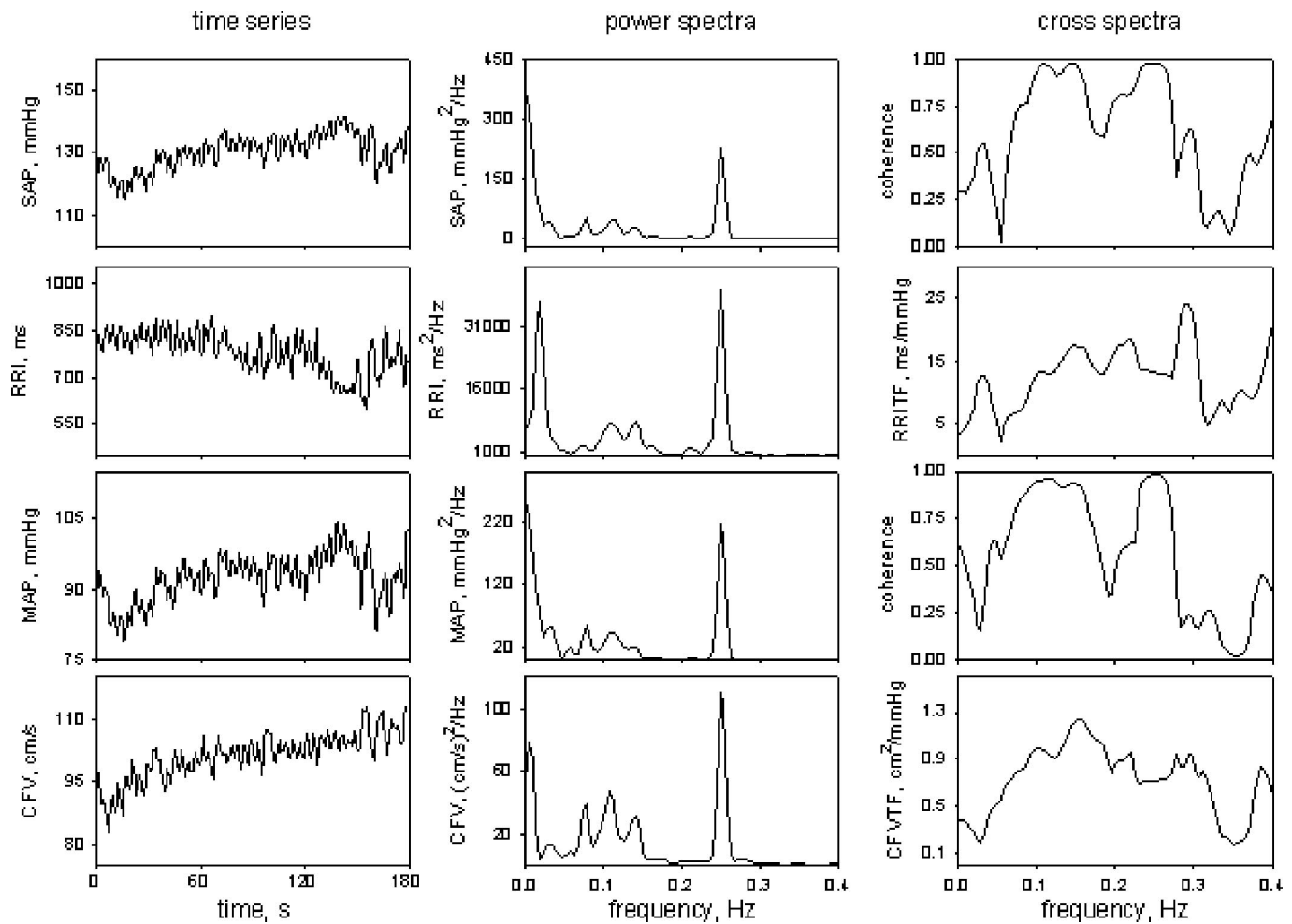
**Fig. 5.** *Frequency domain representations of systolic arterial pressure (SAP), cardiac interbeat intervals (RRI), mean arterial pressure (MAP), and cerebral flow velocity (CFV) shown with cross spectral calculations; R-R interval transfer function (RRITF); cerebral flow velocity transfer function (CFVTF).*

has shown previously that the significant coherence existing in humans between arterial pressure and R-R interval oscillations at the HF disappears when contributions from respiration are removed mathematically,[33] revealing the primary importance of respiration over arterial baroreflex regulation of cardiac interbeat intervals at the HF. Moreover, sinoaortic denervation in rats eliminates coherence between arterial pressure and R-R intervals at the LF, but not HF.[34]

Arterial pressure oscillations occurring at frequencies lower than HF translate into oscillations of R-R intervals at these same frequencies. These beat-to-beat changes in intercardiac intervals are revealed with transfer function analysis between systolic pressure and R-R interval and reflect the sensitivity (or gain) of the cardiovagal baroreflex.[20,35] In a previous investigation, the sensitivity of the reflex cardiac response to direct carotid baroreceptor stimulation was not altered by breathing on an active ITD.[4] Further evidence suggesting that resistive breathing does not modulate autonomic neural function is revealed by our observation of a lack of change in cardiovagal baroreflex sen-

sitivity assessed in the present study with the use of transfer function analysis (Table 2).

## Resistive Breathing and Cerebrovascular Regulation

Dynamic cerebral autoregulation refers to the capacity of the cerebral vascular to regulate on a beat-by-beat basis blood flow velocity to maintain constant or unchanging flow in the face of changes in arterial blood pressure. Dynamic cerebral autoregulation is modulated, in part, by systemic autonomic neural control,[36] and the transfer function between arterial pressure and cerebral blood flow velocity at the LF describes a frequency dependence of dynamic cerebral autoregulation.[21] In the present study, breathing through the active ITD had no effect on transfer function magnitudes among arterial pressures and cerebral blood flow velocities at the LF (Table 2). Therefore, our results provide evidence that inspiratory resistance increases cerebral blood flow velocity without affecting dynamic cerebral autoregulation. This result is not surprising given that the magnitude of increase in mean arterial pressure induced by breathing

on the active ITD is well within the cerebrovascular autoregulatory range for humans.[37]

Although we cannot ascribe a particular underlying mechanism to increases in cerebral blood flow velocity, Marino et al.[7] have shown that active ITD breathing increases cardiac index and stroke volume index in pigs, and Convertino et al.[5] have shown recently that active ITD breathing increases stroke volume and cardiac output in humans. Increases in cerebral blood flow velocity during exercise are associated with increases in cardiac output,[37] and exercise-induced increases in cerebral blood flow velocity are blunted by adrenergic blockade that limits increases in cardiac output during exercise.[38] Although we did not measure cardiac output in the present study, the observed increases in heart rate and arterial pressure are consistent with the findings of Convertino et al.,[5] and therefore it seems reasonable that increases in cerebral blood flow velocity during active ITD breathing are linked, at least in part, to increases in cardiac output. Based on previous experiments, it is reasonable to suggest that increased cardiac output contributes to higher mean arterial pressure (perfusion pressure) and cerebral blood flow during ITD breathing. Increased cardiac output could cause increased cerebral perfusion pressure as observed in pigs by Yannopoulos et al.,[11] and provide an economical explanation for the observed increase in cerebral blood flow velocity in humans. In addition, there exists the possibility of a 'siphon' effect, because previous experiments from Dr. Lurie's laboratory demonstrate that ITD breathing also reduces intracranial pressure. Both observations provide evidence that the mechanism of increased cerebral blood flow is probably a combination of higher cardiac output (and mean arterial pressure) and lower intracranial pressure. In the absence of cardiac output and intracranial pressure measurements that have already been reported, our current experiment focused on testing the hypothesis that cerebral blood flow velocity was increased with ITD breathing: our data support this hypothesis.

We cannot discount the possibility that increased respiratory drive during active ITD breathing increased cerebral metabolic activity and therefore induced cerebral vessel dilation. In the present study, cerebral vascular resistance was estimated by calculating a pulsatility index, and although changes in the pulsatility index were not significant, they tended to decrease with active ITD breathing ($p = 0.09$). End-tidal $CO_2$ was similar during sham and active ITD breathing, but end-tidal $CO_2$ is an imperfect predictor of $Pa_{CO_2}$,[37] and cerebral blood flow velocity changes ~3.5% for every 1 mm Hg change in end-tidal $CO_2$.[39] The possibility of increased cerebral metabolic activity or increased $CO_2$ in venous blood returning to the heart cannot be accounted for in this study, but could have contributed in conjunction with increased cardiac output and lower intracranial pressure to the observed increase in cerebral blood flow velocity.

We speculate that increases in heart rate, arterial pressure, and cerebral blood flow velocity during active ITD breathing occur independent of changes of autonomic neural function as outlined, but we cannot ascribe specific underlying physiologic mechanisms to our observed responses. However, understanding such mechanisms may be of lesser importance than gaining an appreciation for the potential clinical significance of resistive breathing. The ITD has been used by about 100 patients undergoing dialysis who develop hypotension, about 20 patients who have significant orthostatic hypotension, and 18 normotensive volunteers with induced hypotension brought on by a squat-stand test.[12] While most of the data from these studies have not yet been published, the results show a similar physiology: inspiration through a low level of impedance results in a significant increase in systemic pressures, and in many cases decreases or eliminates symptoms associated with hypotension.[12] Reduced symptoms of orthostatic instability are conducive to increases in cerebral perfusion as suggested by the results of the present study.

## Limitations

Although our results suggest that breathing on an active ITD may assist in the stabilization of bleeding patients by maintaining arterial pressure and cerebral blood flow velocity, resistive breathing may not be indicated in all cases. For example, patients with acute respiratory distress, thoracic wall injury, or circulatory/hypovolemic shock syndromes may have markedly reduced respiratory muscle function in conjunction with rapid, shallow breathing. Therefore, it is possible that application of an ITD for these patients may actually impair ventilation and necessitate positive pressure breathing. In the present study, use of an active ITD increased heart rate, arterial pressure, and cerebral blood flow velocity and we speculate that these effects have clinical relevance for the stabilization of bleeding patients, but only for those patients who are able to breathe spontaneously and robustly.

## CONCLUSIONS

Our data suggest that the negative intrathoracic pressures induced by breathing through an active ITD generates a vacuum sufficient to draw blood toward the heart to increase systemic pressures and cerebral blood flow velocity. The increased cardiac filling and consequent stretching of the sinus node increases heart rate and arterial pressure independent of changes in autonomic function. The combined increase of arterial pressure and cerebral blood flow velocity observed in the present study, regardless of physiologic mechanisms underlying such responses, may be conducive to slowing or preventing progression to hemodynamic instability during conditions of central hypovolemia. Such enhancement might assist in the stabilization of bleeding patients awaiting more aggressive medical intervention, but this hypothesis has not been tested specifically.

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